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THE INFLUENCE OF REACTANT STRUCTURE AND SOLVENT ON GALACTOSIDE SYNTHESES FROM GALACTOSYL SULFONATES

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ABSTRACT

The glycosidation of some 2-*O*-allyl- and 2-*O*-benzyl-D-galactopyranosyl sulfonates was studied as a function of alcohol, solvent, leaving group at C-1, and substituent groups at C-3, -4, and -6. In the 2,3,4-tri-*O*-benzyl series, no combinations of these parameters lead to high α-stereoselectivity, and high β-stereoselectivity was observed only in methanolyses with the trifluoromethanesulfonate leaving-group. With 2,3-di-*O*-benzyl-4,6-di-*O*-(*N*-phenylcarbamoyl)-D-galactopyranosyl *p*-toluenesulfonate, high α-specificity (>90%) was achieved on methanolysis and, with the corresponding trifluoromethanesulfonate, high β-stereoselectivity. Results with 2-*O*-allyl- and 2-*O*-benzyl-3,4-di-*O*-(*N*-phenylcarbamoyl)-6-*O*-acetyl-D-galactopyranosyl sulfonates were comparable to each other. In general methane- and *p*-toluenesulfonates in solvents of the ether type gave high α-stereoselectivity (>90%) with a number of alcohols of widely different structures, including saccharides. Thus, appropriately substituted D-galactopyranosyl sulfonates, reacting overnight with an equivalent amount of alcohol, formed α-glycosides in high yield and steric purity, as has previously been observed with related glucose derivatives. The nature of the substituents at C-3, C-4, and C-6 has a profound influence on the steric course of the glycosidation reaction.

INTRODUCTION

At least since the 1960 contribution of Rhind-Tutt and Vernon[1], the glycoside-forming reaction of glycosyl halides has been treated as the nucleophilic attack of an alcohol on a labile ion-pair. In the absence of neighboring-group participation, the alcohol is assumed to approach the glycosyl cation from the rear side and thus produce a glycoside having the configuration opposite to that of the tight ion-pair. In general, the thermodynamically favored α-glycosyl halide is much less reactive than the β ion-pair, so that some degree of isomerization of the α halide usually occurs prior to reaction, and a mixture of β- and α-glycosides results[2]. By increasing the concentration of halide ion relative to that of alcohol, Lemieux and coworkers[3] have, in several cases, been able to cause sufficient inversion of an α-glycosyl bromide

prior to glycosidation to obtain α-glycosides of rather high anomeric purity. In this laboratory, we have been investigating the influence of alcohol concentration, substituent groups, sugar structure, leaving group, and solvent on the stereoselectivity of glycoside-forming reactions[4-15]. In our experience, high concentration of alcohol always tends to favor formation of the β-glycoside or to decrease α-stereoselectivity. If the customary halide leaving-groups are avoided, and sulfonates are used instead, an attractive series of groups of widely differing reactivities is available: methane-, *p*-toluene-, benzene-, *p*-bromobenzene-, 2,2,2-trifluoroethane-, and trifluoromethanesulfonate, and so on. Apparently, all of these are more reactive as leaving groups than bromide and, in the examples we have tried, reaction between one mole of glycosyl sulfonate with slightly more than one mole of alcohol in homogeneous solution results in essentially complete reaction during periods ranging from a few min to a few h[6,11,13,14]. If silver sulfonate is allowed to react with a glycosyl halide in the presence of alcohol, the steric course of these reactions sometimes differs from that observed when the sulfonate is preformed[6]. Therefore, for consistency and simplicity, in these experiments, we first allowed the glycosyl halide to react completely with silver sulfonate and then added an alcohol to the resultant product in homogeneous solution. The stereoselectivity is then dependent on the glycosyl-group structure, the leaving group and pattern of substituents, and the solvent in which the reaction is conducted. In previous research, it was shown that 2,3,4-tri-*O*-benzyl-6-*O*-(*N*-phenylcarbamoyl)-1-*O*-*p*-toluenesulfonyl-D-glucopyranose reacted in ether with alcohols to form α-glycosides in high steric purity[11], and that the reaction could be readily used in the stepwise synthesis of isomalto-oligosides[13]. In an attempt to extend this result to D-galactose, 2,3,4-tri-*O*-benzyl-D-galactopyranose derivatives having at C-1 the *p*-toluene-, *p*-bromobenzene-, and trifluoromethane-sulfonate leaving-groups and at *O*-6 the benzyl, *N*-phenylcarbamoyl, *N*-(*p*-methoxyphenyl)-carbamoyl, *p*-nitrobenzoyl, and 3-acetylpropionyl protecting groups, were subjected to methanolysis with one equivalent of methanol in various solvents. The results were disappointing[14]. Formation of α-glycoside was highest with the *p*-toluenesulfonate leaving-group, but in no instance was the stereoselectivity high enough to be of interest. The *p*-bromobenzenesulfonate leaving-group, in limited testing, gave rather more β-glycoside, and the trifluoromethanesulfonate group in a few examples gave high β-stereoselectivity. However the β-stereoselectivity was adversely affected by complexity of the aglycon when the reactions were tested under similar conditions in the synthesis of disaccharides[14]. The following experiments were undertaken to determine whether more-successful glycoside syntheses could be effected with other galactose derivatives.

RESULTS AND DISCUSSION

Our previous results on 2,3,4-tri-*O*-benzyl-D-galactopyranose derivatives[14] were extended by investigating the effects of the aglycon, the solvent, and some C-1 and C-6 substituents on the stereochemical outcome of glycosidation reactions. The

TABLE I
GLYCOSIDATION OF 2,3,4-TRI-*O*-BENZYL-D-GALACTOPYRANOSYL DERIVATIVES

6-O-Substituent	*Alcohol*[a]	*Solvent*	*Conversion* (%)	*α Anomer* (%)
1-*p*-Toluenesulfonate[b]				
N-Phenylcarbamoyl	A[c]	Acetonitrile	75	57
N-Phenylcarbamoyl	A[c]	Diethyl ether	73	44
N-Phenylcarbamoyl	A	Acetonitrile	100	33
N-Phenylcarbamoyl	A	Diethyl ether	100	37
N-Phenylcarbamoyl	B	Acetonitrile	100	44
N-Phenylcarbamoyl	B	Diethyl ether	100	30
N-Phenylcarbamoyl	C	Acetonitrile	100	30
N-Phenylcarbamoyl	C	Diethyl ether	100	37
p-Toluenesulfonyl		Acetonitrile	100	Baseline
p-Toluenesulfonyl	A	Acetonitrile	100	36
p-Toluenesulfonyl	A	Diethyl ether	70	21
p-Toluenesulfonyl	E	Acetonitrile	67	50
p-Toluenesulfonyl	E	Diethyl ether	100	21
p-Toluenesulfonyl	B	Acetonitrile	100	44
p-Toluenesulfonyl	B	Diethyl ether	91	22
1-Trifluoroethanesulfonate[b]				
p-Toluenesulfonyl	A	Acetonitrile	85	42
p-Toluenesulfonyl	A	Diethyl ether	100	10
p-Toluenesulfonyl	E	Acetonitrile	100	37
p-Toluenesulfonyl	E	Diethyl ether	100	19
p-Toluenesulfonyl	B	Acetonitrile	63	21
p-Toluenesulfonyl	B	Diethyl ether	100	27
p-Toluenesulfonyl	C	Acetonitrile	100	33
p-Toluenesulfonyl	C	Diethyl ether	85	22
1-Trifluoromethanesulfonate[d]				
(*p*-Methoxyphenylcarbamoyl)	A[c]	Dichloromethane	93	15
	A	Dichloromethane	87	28
N-Phenylcarbamoyl	A	Dichloromethane	94	6
p-Toluenesulfonyl	A	Dichloromethane	92	9
p-Toluenesulfonyl	A	Diethyl ether	100	14
p-Toluenesulfonyl	A	Dimethoxyethane (−58°C)	71	15
p-Toluenesulfonyl	A	Tetrahydrofuran	100	61
p-Toluenesulfonyl	B	Dichloromethane	84	36
p-Toluenesulfonyl	B	Diethyl ether	100	12
N-Phenylcarbamoyl (alcohol = methyl 2,3,4-tri-*O*-benzyl-α-D-galactopyranoside)		Dichloromethane	52	56
N-Phenylcarbamoyl (alcohol = methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside)		Dichloromethane	72	46

[a]A = methanol, B = isobutyl alcohol, C = cyclohexanol, E = ethanol. One equivalent used. [b]Trifluoroethane- and *p*-toluene-sulfonate reactions conducted at room temperature. [c]Results from ref. 14.[d]Trifluoromethanesulfonate reactions conducted at −78° unless stated otherwise.

starting materials and reactants were prepared by conventional methods and the reactions were conducted on preformed glycosyl sulfonates and approximately equivalent amounts of alcohol. The results are reported in Table I. Some experimental improvements were introduced into our earlier techniques to ensure anhydrous

conditions, and as a result the yields are better than those of Lucas and Schuerch[14]; they show essentially complete reaction. The few non-quantitative yields probably reflect errors in measurement of the alcohol or the slower formation of the 6-*O*-*p*-toluenesulfonyl-glycosyl chloride, the precursor of the 1-sulfonate.

Two new substituents were tested in this series, the 6-*O*-toluenesulfonyl and the 2,2,2-trifluoroethanesulfonate leaving-groups at C-1. The results obtained with the latter were similar to those with the *p*-toluenesulfonate leaving-group. All reactions were conducted at room temperature, except for those with the trifluoromethanesulfonate group, which proceeded at decreased temperature. The solvent-dependence of the reactions of 6-*O*-*p*-toluenesulfonylgalactopyranose derivatives was greater, in general, than that of the 6-*O*-(*N*-phenylcarbamoyl)-D-galactopyranose derivatives, irrespective of the substituent at C-1. In contrast to the results found by Eby[11] on corresponding glucose derivatives, those reactions effected in acetonitrile on the 6-*O*-*p*-tolylsulfonyl-D-galactopyranosyl sulfonates produced more α anomer than those performed in ether.

The stereoselectivity found in this series was highest for formation of β-glycoside when the leaving-group at C-1 was trifluoromethanesulfonate and decreased in the order $F_3C\text{-}SO_3\text{-} > F_3C\text{-}CH_2\text{-}SO_3\text{-} \simeq p\text{-}CH_3C_6H_4SO_3\text{-}$. None of the reactions led to high α-stereoselectivity. These results in general confirm and extend the results of Lucas and Schuerch[14]. Furthermore, those reactions that favored formation of high proportions of β-glycoside with methanol were much less selective with saccharides. It, therefore, seems clear that derivatives having this substitution pattern are not attractive reactants in stereoselective syntheses of galactosides. Similarly Fréchet and Baer have found that both 2,3,4,6-tetra-*O*-benzyl- and 2,3,4-tri-*O*-benzyl-6-*O*-*p*-nitrobenzoyl-α-D-galactopyranosyl bromide fail to give high α-stereoselectivity on methanolysis with excess methanol, even with catalysis by bromide ion[16].

Leaving this series, a limited number of methanolyses were conducted on 2,3-di-*O*-benzyl-4,6-di-*O*-(*N*-phenylcarbamoyl)-D-galactopyranosyl *p*-toluenesulfonate. (Table II). This compound may be prepared in a straightforward sequence from allyl 4,6-*O*-benzylidene-α-D-galactopyranoside. It and others to be discussed were chosen because substituents[17] at C-4 and, apparently to a lesser extent, C-3 in other series[18], have been shown to affect stereoselectivity of reactions at C-1. This influence proved to be the case here as, in contrast to the results with 2,3,4-tri-*O*-benzyl-D-galactopyranosyl *p*-toluenesulfonate, this compound gave rather high α-selectivity on methanolysis in ethers. In dimethoxyethane, about 94% of the α-product was formed. In the same solvent, 2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl *p*-toluenesulfonate, for example, gave only 43% of α-glycoside. Furthermore, methanolysis of 2,3-di-*O*-benzyl-4,6-di-*O*-(*N*-phenylcarbamoyl)-1-*O*-trifluoromethanesulfonyl-D-galactopyranose in ether at $-70°$ gave, according to n.m.r.-spectral analysis, essentially no α, and only the β anomer. Clearly, these galactopyranose derivatives show much more promise in stereoselective glycoside syntheses.

These results were generally confirmed when galactopyranose derivatives having ether substituents only at C-2 were tested (Table III). In previous work from

TABLE II

METHANOLYSIS OF 2,3-DI-*O*-BENZYL-4,6-DI-*O*-(*N*-PHENYLCARBAMOYL)-α-1-*O*-TOSYL-D-GALACTOPYRANOSE

Solvent	*α:β Ratio*	*α (%)*
Ether	15:11	58
Acetonitriie	30:17	64
Dichloromethane	5:13	28
Dimethoxyethane	44:3	94
Tetrahydrofuran	8:6	57
1,4-Dioxane	13:2	87

TABLE III

GLYCOSIDATION OF 3,4-DI-*O*-(*N*-PHENYLCARBAMOYL)-6-*O*-ACETYL-D-GALACTOPYRANOSYL DERIVATIVES

1-Sulfonate	*2-O-Substituent*	*Alcohol*[c]	*Solvent*	*Conversion (%)*	*α Anomer (%)*
p-Toluene[a,b]	benzyl	A	acetonitrile	75	69
p-Toluene[a]	benzyl	A	dichloromethane	90	71
p-Toluene[b]	benzyl	A	tetrahydrofurane	89	81
p-Toluene[b]	benzyl	A	1,4-dioxane	75	85
p-Toluene[a]	benzyl	A	ether	84	91
p-Toluene[a]	benzyl	A	dimethoxyethane	91	93
p-Toluene[b]	benzyl	A	dimethyl ether	85	62
p-Toluene[a]	benzyl	B	acetonitrile	95	78[d]
p-Toluene[a]	benzyl	B	dimethoxyethane	95	91[d]
p-Toluene[a]	benzyl	C	acetonitrile	95	80[d]
p-Toluene[a]	benzyl	C	ether	95	88[d]
p-Toluene[b]	allyl	A	acetonitrile		78[d]
p-Toluene[b]	allyl	A	dimethoxyethane		94[d]
Methane[b]	allyl	A	acetonitrile		78[d]
Methane[b]	allyl	A	dimethoxyethane		94[d]
Methane[a]	benzyl	A	acetonitrile	91	65
Methane[a]	benzyl	A	dimethoxyethane	60	92
2,2,2-Trifluoroethane[a]	benzyl	A	acetonitrile	74	58
2,2,2-Trifluoroethane[a]	benzyl	A	dimethoxyethane	86	83
Trifluoromethane[b,e]	allyl	A	ether		26[d]
Trifluoromethane[a,f]	benzyl	A	dichloromethane	58	49
Trifluoromethane[a,f]	benzyl	A	dimethoxyethane	64	33

[a]Prepared from the corresponding galactosyl chloride. [b]Prepared from the corresponding galactosyl bromide. [c]A methanol, B isobutyl alcohol, C cyclohexanol. Concentration of alcohol 0.2mol/l. (One equivalent used.) [d]Anomeric ratios determined from ^{13}C spectrum. [e]Reaction performed at −70°. [f]Reaction performed at −50°.

this laboratory, only the benzyl group has been used[15] as a nonparticipating group on C-2. In this series, the allyl group was also used. It, of course, offers a potential route to 2-substituted oligosaccharides as it can be removed by quite specific reagents under mild conditions[19,20]. The compounds used in the following series are either

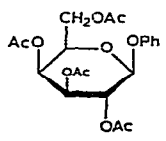
2-*O*-allyl- or 2-*O*-benzyl-3,4-di-*O*-(*N*-phenylcarbamoyl)-6-*O*-acetyl-D-galactopyranosyl sulfonates.

Our attempts to use the procedure of Hodge and Rist[21], who prepared 2-*O*-benzyl derivatives of D-glucopyranose, for the preparation of galactose analogues were unsuccessful. Other methods for preparation of 2-*O*-benzyl-D-galactopyranose and its derivatives have been reported[22–24].

An entry into the series is available from 1,6-anhydro-3,4-*O*-isopropylidene-β-D-galactopyranose (**3**). Benzylation or allylation of **3** gave the corresponding 2-ethers **4** and **5**, respectively. The isopropylidene groups were hydrolyzed, giving the diol **6** and **7**, which were treated with phenyl isocyanate yielding 3,4-di-*N*-phenylcarbamates **8** and **9**, respectively. Acetolysis of **8** and **9** gave the corresponding 1,6-diacetates, **10** and **11**. The glycosyl halides were prepared by reaction of **10** and **11** with hydrogen chloride or hydrogen bromide in dichloromethane or dichloromethane–diethyl ether solution. To counter debenzylation, which has also been observed in the preparation of 1,3,4,6-tetra-*O*-acetyl-2-*O*-benzyl-α-D-galactopyranose[23], the bromide product was filtered through silicic acid before use. However, this procedure resulted in greatly decreased overall yields in comparison with that obtained from the chloride analogue. The chloride is, therefore, the preferred reactant.

Glycosidation was performed as previously described[11,14], with galactopyranosyl derivatives prepared by treatment *in vacuo* of the silver salts of various sulfonic acids with the appropriate galactosyl halide.

Seven different systems gave 91 ±3% of α-galactosides in the anomeric products. (Table III). The overall conversions were also usually 85–95%. Both solvent and leaving-group at C-1 exert a major effect on the anomeric ratio of the products. Such solvents as benzene and carbon tetrachloride were not sufficiently polar to dissolve the *p*-toluenesulfonates, so that only more-polar solvents could be used. Of these, the ethers, especially 1,2-dimethoxyethane, yielded the highest proportion of α products. The effect of the nature of solvent is practically the same as that observed in methanolyses of 6-*O*-substituted-2,3,4-tri-*O*-benzyl-D-glucopyranosyl *p*-toluene-



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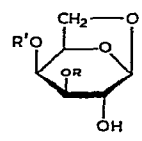
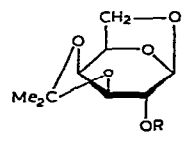


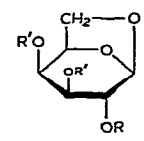
2 R = R' = H

3 R, R' = Me_2C



4 R = $PhCH_2$

5 R = $H_2C{=}CHCH_2$

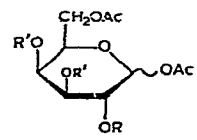


6 R = $PhCH_2$, R' = H

7 R = $H_2C{=}CHCH_2$, R' = H

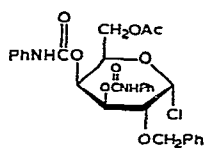
8 R = $PhCH_2$, R' = PhNHCO

9 R = $H_2C{=}CHCH_2$, R' = PhNH



10 R = $PhCH_2$, R' = PhNHCO (α anomer)

11 R = $H_2C{=}CHCH_2$, R' = PhNHCO



12

sulfonate[11]. The effect of the leaving group was also generally consistent with results of related, previous work. Specificity for α-glycoside was in the order: p-$CH_3C_6H_5SO_3$- > F_3C-CH_2-SO_3- > F_3C-SO_3-. However, substitution of methane- and p-toluenesulfonate groups were practically equally stereoselective. It was also encouraging to find that the 2-*O*-allyl and 2-*O*-benzyl groups could be used interchangeably, without diminution of the yield of α product, and the stereoselectivity of the reaction was reasonably insensitive to the structure of reactant alcohol (methanol, cyclohexanol, and isobutyl alcohol).

Disaccharides were also prepared by treatment of 6-*O*-acetyl-2-*O*-benzyl-3,4-di-*O*-(*N*-phenylcarbamoyl-D-galactopyranosyl p-toluenesulfonate with methyl 2,3,4-tri-*O*-benzyl-D-galacto-(and D-manno-pyranoside in 1,2-dimethoxyethane. In both instances, the same ratio of α anomers was obtained as with simpler alcohols (89 and 91% respectively), but the yield was relatively low (~55% of theoretical). The reasons for the lower yield were not explored because of a shortage of reagent. However, it is believed that minor differences in technique may have led to these poorer yields and, with further experience, results comparable to those with simple alcohols may be obtained, most probably at longer reaction-times.

In summary, it appears that glycoside syntheses of high α-stereoselectivity can be achieved with the 2-*O*-allyl- and 2-*O*-benzyl-D-galactopyranosyl p-toluene- and methane-sulfonates tested and probably with similar 2,3-di-*O*-benzyl derivatives. The sensitivity of their glycosidation reactions to solvents and their relative insensitivity to aglycon (alcohol) structure is reminiscent of the behavior of 2,3,4-tri-*O*-benzyl-D-glucopyranosyl p-toluenesulfonate. These properties suggest the suitability of these and related compounds for the production of α-galactosidic linkages in oligosaccharides.

EXPERIMENTAL

General. — Melting points were determined with a "Meltemp" instrument and 76-mm immersion thermometer, and are recorded as read. Optical rotations were performed at ambient temperature, usually in chloroform at a concentration of about 1 g/100 ml, with a Perkin–Elmer 141 automatic polarimeter. N.m.r. spectra were determined in chloroform-*d* solutions with Varian A-60-A or XL-100 spectrometers. Elemental analyses were performed by Galbraith Laboratories, Inc. Thin-layer chromatography (t.l.c.) was performed on silica gel plates (Bakerflex 1B-F) and sprayed when necessary with sulfuric acid–ethanol (~1:3). Column chromatography was performed as needed on silicic acid (Mallinckrodt No. 2844) or neutral alumina (Brockmann activity 1, Fischer Scientific).

*Preparation of 2,3,4-tri-*O*-benzyl-*D*-galactopyranosyl derivatives.* — Methyl 2,3,4-tri-*O*-acetyl-6-*O*-trityl-α-D-galactopyranoside was prepared by sequential tritylation and acetylation of methyl α-D-galactopyranoside, and was converted into the 2,3,4-tri-benzyl ether with potassium hydroxide and benzyl chloride. Detritylation with hydrogen bromide in acetic acid was not complete, but subsequent acetolysis

with acetic anhydride and sulfuric acid gave 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-α,β-D-galactopyranose. Catalytic deacetylation with sodium methoxide in methanol produced 2,3,4-tri-*O*-benzyl-α-D-galactopyranose, which was separated from some impurities by chromatography on an alumina column. Elution with chlorinated solvents and diethyl ether removed impurities, and the desired product was then extracted with methanol. 2,3,4-Tri-*O*-benzyl-α-D-galactopyranose was crystallized from diethyl ether–petroleum ether as a white solid, m.p. 72–74°, $[\alpha]_D^{25}$ +70.8° (*c*, 0.9, ether); lit.[25], m.p. 70–71°, $[\alpha]_D^{25}$ 72.5° (*c*, 0.8 ether). The preparation of 2,3,4-tri-*O*-benzyl-1,6-di-*O*-(*p*-methoxy-*N*-phenylcarbamoyl)-D-galactopyranose after Lucas and Schuerch[14] gave a mixture of isomers having a wide melting range, beginning at 111°; $[\alpha]_D^{25}$ +4.56° (*c* 1, chloroform). The 1,6-di-*O*-(*N*-phenylcarbamoyl)-2,3,4-tri-*O*-benzyl-D-galactopyranose obtained was largely or completely the β anomer, having m.p. 167–169°, $[\alpha]_D^{25}$ −2.5° (*c* 1.15, chloroform). Both products had p.m.r. spectra consistent with their structures. Tosylation of 2,3,4-tri-*O*-benzyl-α-D-galactopyranose (2 g, 4.4 mmol) in 2,6-dimethylpyridine (30 ml) with *p*-toluenesulfonyl chloride (3.41 g, 1.79 mmol) proceeded for 6 days at room temperature. Hydrolysis, extraction into benzene, washing with acid, drying, and chromatography on silicic acid yielded 2.11 g (80%) of syrup, $[\alpha]_D^{25}$ +32.85 (*c* 1.3, chloroform) and unreacted starting material (0.414 g). This product (1.76 g, 2.9 mmol) was dissolved in dry pyridine (50 ml), and phenyl isocyanate (0.4 g, 3.4 mmol) was added at 0–5°C. The reaction was maintained for 30 min at this temperature, for 30 min at room temperature and for 30 min at 80°. The mixture was diluted with 200 ml of water, extracted with dichloromethane, and the solution evaporated to a syrup from which water was distilled to remove pyridine. Extraction with hot, dry benzene allowed diphenylurea to precipitate. Filtration and crystallization of the syrup remaining after concentration yielded (from ethanol–water) 1.5 g (73%) of 6-*O*-*p*-toluenesulfonyl-2,3,4-tri-*O*-benzyl-1-*O*-(*N*-phenylcarbamoyl)-β-D-galactopyranose, $[\alpha]_D^{25}$ −23.4° (*c* 1.0, chloroform). Recrystallization from 100% ethanol gave 0.973 g (46%), m.p. 144.5–145° (decomp.), $[\alpha]_D^{25}$ −7.14° (*c*, 0.9, chloroform).

Anal. Calc. for $C_{41}H_{41}NO_9S$: C, 68.03; H, 5.71; N, 1.93. Found: C, 67.85; H, 5.87; N, 1.93.

Preparation of 6-O-substituted-2,3,4-tri-O-benzyl-α-D-galactopyranosyl chlorides and their conversion into sulfonates and glycosides. — The 6-*O*-substituted 2,3,4-tri-*O*-benzyl-D-galactopyranosyl chlorides were prepared by the method of Kronzer and Schuerch from the corresponding 6-*O*-substituted 1-*O*-(*N*-phenylcarbamoyl)-galactopyranosyl derivatives, using hydrogen chloride in the place of hydrogen bromide. The galactosyl chlorides were obtained as syrups and were dried thoroughly under high vacuum prior to use. The chloride was then treated, under high vacuum as described by Lucas and Schuerch[14], for 30 min with a silver sulfonate to form the corresponding derivative. Subsequent reaction of the preformed derivatives with equivalent amounts of the alcohols was allowed to proceed overnight in the case of the *p*-toluene- and trifluoroethane-sulfonates and for 30 min with the trifluoromethanesulfonate. At the end of the designated time, the mixtures were diluted with dichloromethane and

extracted with saturated sodium hydrogencarbonate, aqueous sodium thiosulfate, and distilled water. The organic extracts were dried (sodium sulfate) and evaporated to syrups. N.m.r. spectra were taken directly on the syrups dissolved in deuteriochloroform.

For disaccharide synthesis, the procedure just outlined was modified in that the methyl 2,3,4-tri-*O*-benzyl-α-D-galacto- and manno-pyranosides were dried in a second chamber. The preformed trifluoromethanesulfonates were then filtered onto these compounds *in vacuo* and reaction was allowed to proceed at −78°. The mixtures were processed as described previously, and the crude syrups obtained were chromatographed on silicic acid. The total conversion and percent of each anomer were estimated from ^{13}C spectra. The coupling of the 6-*O*-(*N*-phenylcarbamoyl)-2,3,4-tri-*O*-benzyl-D-galactopyranosyl trifluoromethanesulfonate with methyl 2,3,4-tri-*O*-benzyl-α-D-galactopyranoside yielded 52.3% of disaccharides (α:β = 14:11). The corresponding coupling with methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside yielded 71.9% of disaccharides (α:β = 23:27; ^{13}C n.m.r. C-1α 99.35, C-1β 104.57). The latter disaccharide crystallized from diethyl ether–petroleum ether; yield of crystalline methyl 6-*O*-(*N*-phenylcarbamoyl)-2,3,4-tri-*O*-benzyl-β-D-galactopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-mannopyranoside 0.107 g (0.105 mmol, 5.5%); m.p. 108.5–110°, $[\alpha]_D^{25}$ +4.71 (*c* 1.02, chloroform).

Calculation of anomeric ratio and conversion in glycosidation. — The ratio of methyl glycosides in the glycosidation product was determined by comparison of peak areas of to the two glycosidic methoxyl groups in the proton-n.m.r. spectra of the organic-soluble fraction from processing of the glycosidation reaction. A baseline correction was applied from a spectrum obtained from the product of reaction with methanol-d_4. As unreacted glycosyl sulfonate should appear in the product fraction hydrolyzed to give the hydroxyl group, the percent conversion was calculated from the ratio of peak areas for glycosidic methoxyl hydrogen to that for aromatic hydrogen. When these data were compared with those obtained from anomeric-peak intensities for the corresponding species in the ^{13}C n.m.r. spectra, good agreement was generally obtained. The latter method was, therefore, applied to glycosides of higher alcohols that could not be conveniently analyzed by proton-n.m.r. spectroscopy.

*Preparation of 2,3-di-*O*-benzyl-4,6-di-*O*-(*N*-phenylcarbamoyl)-α-D-galactopyranosyl bromide.* — (By Mr. Paul Morris). 1-*O*-Allyl-α-D-galactopyranoside was prepared by a Fischer synthesis[26], converted into the known 4,6-benzylidene acetal[27], and benzylated with potassium hydroxide and benzyl chloride by known methods. Debenzylidenation with acetic acid and water[28a] yielded an oil that was carbanilated with phenyl isocyanate in pyridine. Purification by chromatography gave the 4,6-di-*O*-(*N*-phenylcarbamoyl) derivative having m.p. 167–170°, $[\alpha]_D$ −7.7° (chloroform). Rearrangement of the allyl to the propenyl group, and hydrolysis with acetic acid and water, gave the free sugar; m.p. 197–203°, $[\alpha]_D$ +16.5° (acetone). This was converted into the 1,4,6-tri-*O*-(*N*-phenylcarbamoyl) derivative and thence as previously into the glycosyl bromide with hydrogen bromide in acetic acid. The bromide was filtered through silicic acid before use, and converted into the desired *p*-toluene-

sulfonate and glycoside. Filtration through silicic acid was necessary to remove material debenzylated by hydrogen bromide, so that overall yields were lower than in the other series. All compounds through the dicarbanilate had n.m.r. spectra consistent with their proposed structures.

Preparation of 1,6-anhydro-2-O-benzyl-β-D-galactopyranose (**6**). — Phenyl tetra-*O*-acetyl-β-D-galactopyranoside (**1**) was prepared from penta-*O*-acetyl-β-D-galactopyranose (Senn Chemicals) in several batches of 125 g with yields 41.6%, m.p. 121.5–122°, $[\alpha]_D$ +3.98 to −0.5° (*c* 1, chloroform) lit.[29], m.p. 123°–124°, $[\alpha]_D^{20}$ −0.7° (chloroform). Crude phenyl β-D-galactopyranoside from deacetylation of **1** was directly cyclized to give 1,6-anhydro-β-D-galactopyranose[30,31] (**2**). The product was crystallized from 2:1 acetone–methanol; yield 51.5% (calc. on the basis of **1**), m.p. 220–221°, $[\alpha]_D$ −22.2 (*c* 1, water); lit.[32] m.p. 220–221°, $[\alpha]_D^{21}$ −21.9° (water).

Dry, powdered (**2**) (30 g) was stirred with dry acetone (900 ml) and dry copper sulfate (300 g). At the beginning, a small amount of dry hydrogen chloride was bubbled through the mixture. After 72 h copper sulfate was filtered off and extracted with hot acetone. The acetone solutions were collected and evaporated to dryness, and the residue was extracted with dry chloroform under reflux. The extracts were treated with Darco and evaporated to 100 ml. The resulting crystals were recrystallized from chloroform–hexane. The 1,6-anhydro-3,4-di-*O*-isopropylidene-β-D-galactopyranose (**3**) isolated yield 34.1 g (91.2%) had 153–154°, $[\alpha]_D$ −73.2°, (*c* 1, chloroform); lit.[28b], m.p. 151–152°, $[\alpha]_D^{19}$ −73° (*c* 1.7, chloroform).

A solution of **3** (0.168 mol) in dry toluene (180 ml) was heated for 4 h at 120° under reflux and stirring with benzyl chloride (0.67 mol) and powdered potassium hydroxide (0.42 mol), and was then kept overnight at room temperature. Solvents were evaporated off under diminished pressure and the residue was extracted with chloroform. The solution was washed with water, dried, and evaporated to dryness. The crude 1,6-anhydro-2-*O*-benzyl-3,4-*O*-isopropylidene-β-D-galactopyranose (**4**) was twice crystallized from abs. ethanol; yield 41.9 g (85.4%), m.p. 81–82°, $[\alpha]_D$ −81.9° (*c* 1, chloroform); lit.[22] m.p. 84–84°, $[\alpha]_D^{22}$ −81.9° (*c* 0.87, chloroform).

The solution of (**4**) (35 g) in ethanol (450 ml, 65%) containing sulfuric acid (4 mmol) was boiled for 10 h under reflux. After neutralization, the solvents were distilled off and abs. ethanol was distilled from the residue. Crude 1,6-anhydro-2-*O*-benzyl-β-D-galactopyranose (**6**) was extracted with dichloromethane and crystallized after addition of petroleum ether; yield 28.6 g (94.7%) of colorless plates, m.p. 102.5–103.5°, $[\alpha]_D$ −37.4°, (*c* 1, chloroform); lit.[22], m.p. 104–105°.

Preparation of 1,6-anhydro-2-O-allyl-β-D-galactopyranose (**7**). — 1,6-Anhydro-2-*O*-allyl-3,4-*O*-isopropylidene-β-galactopyranose (**5**) was prepared by the same method as for the benzyl analog, with the modification that allyl bromide was used as both reagent and solvent. The product was crystallized from ether–petroleum ether in 73% yield, m.p. 55–56°, $[\alpha]_D$ −74°, (chloroform).

Anal. Calc. for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.67; H, 7.65. Compound **7** was obtained as a syrup in 100% yield; $[\alpha]_D$ −27.5°, (*c* 1, chloroform).

Anal. Calc. for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.28; H, 6.86.

1,6-Anhydro-2-O-benzyl-3,4-di-O-(N-phenylcarbamoyl)-β-D-galactopyranose (**8**). — Phenyl isocyanate (31.8 g) was added dropwise to a solution of **6** (28.3 g) in dry pyridine (150 ml) at 0° with stirring. After 72 h, water (1 ml) was added and the solution was then poured onto ice. The organic portion was extracted with chloroform, washed with water, and dried. The solvents were distilled off under diminished pressure and toluene was distilled from the residue. The residue was extracted with the same solvent, and the mixture filtered. Toluene was distilled off and the product was crystallized from dry ether; yield 44.7 g (81.3%) of colorless needles m.p. 105° (transition at 78–80°), $[\alpha]_D$ −99.9°, (*c* 1, chloroform).

Anal. Calc. for $C_{27}H_{26}N_2O_7$: C, 66.11; H, 5.34; N, 5.71. Found: C, 65.99; H, 5.47; N, 5.69.

1,6-Anhydro-2-O-allyl-3,4-di-O-(N-phenylcarbamoyl)-β-D-galactopyranose (**9**). — This product was crystallized from ether–petroleum ether; yield 90%, m.p. 79–80°, $[\alpha]_D$ −61.6°, (*c* 1, chloroform).

Anal. Calc. for $C_{23}H_{24}N_2O_7$: C, 62.72; H, 5.49; N, 6.36. Found: C, 62.67; H, 5.68; N, 6.16.

1,6-Di-O-acetyl-2-O-benzyl-3,4-di-O-(N-phenylcarbamoyl)-α-D-galactopyranose (**10**). — To a solution of **8** (10 g) in acetic anhydride (25 ml), was added a solution of sulfuric acid (1 mmol) in acetic anhydride (5 ml) at 0° with stirring. After 10 min, the mixture was poured onto ice and, after decantation, stirred with water (800 ml) overnight. The precipitate was filtered off and dissolved in chloroform. The solution was washed with water and sodium hydrogencarbonate solution, dried (magnesium sulfate), and evaporated to dryness under diminished pressure. The resulting, glassy product was crystallized twice from 1 : 1 ethanol–hexane; yield 8.1 g (67%) of colorless crystals, m.p. 163–164° (transition at 148°), $[\alpha]_D$ +103.9°, (*c* 1, chloroform).

Anal. Calc. for $C_{31}H_{32}N_2O_{10}$: C, 62.83; H, 5.44; N, 4.73. Found: C, 62.82; H, 5.30; N, 4.94.

1,6-Di-O-acetyl-2-O-allyl-3,4-di-O-(N-phenylcarbamoyl)-D-galactopyranose(**11**) — This product was isolated as a syrup in 95% yield.

Anal. Calc. for $C_{27}H_{30}N_2O_{10}$: C, 59.77; H, 5.57; N, 5.16. Found: C, 59.49; H, 5.53; N, 5.15.

6-O-Acetyl-2-O-benzyl-3,4-di-O-(N-phenylcarbamoyl)-α-D-galactopyranosyl chloride (**12**). — After drying under high vacuum, compound **10** (4.8 g) was dissolved in dry dichloromethane (15 ml) and then ether (75 ml) was added. The solution was saturated with dry hydrogen chloride at 0° and kept overnight at room temperature. The solvents were evaporated off under diminished pressure and dry benzene was distilled 4 times from the residue, which was then dried under high vacuum. The crude product was twice crystallized from 3:2 ether–hexane; yield 4.0 g (86.8%) colorless crystals m.p. 154–157° under decomp., $[\alpha]_D$ 139.3°, (*c* 1, chloroform).

Anal. Calc. for $C_{29}H_{29}N_2O_8Cl$: C, 61.21; H, 5.14; N, 4.92; Cl, 6.23. Found: C, 61.50; H, 5.40; N, 4.86; Cl, 6.29.

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